RECENT KNOWLEDGE OF EPIDEMICS

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We are all interested in one way or another in epidemiology and have asked ourselves some of its most perplexing questions. Why do certain diseases suddenly attack a number of individuals at the same time; why do they affect some and spare others; why do they spread—sometimes among a few and sometimes over a greater part of the world; why do they stop; and finally, why do they reappear after an interval of time and repeat the same series of events?

Answers to these questions have not been wanting. Had we lived in the time of Hippocrates we should have looked to the heavens for the cause of pestilence and should have assigned to comets, unusual configurations of the plants, and any remarkable natural phenomena, complete responsibility for epidemic disease. Later, in Sydenham's time, we should have dropped our eyes to the ground and considered noxious vapors and seepings from the soil as causing the trouble. At present, however, Pasteur's hypothesis is generally accepted, and we have come to regard all the varied phenomena of infectious disease as due directly or indirectly to the microbe. An epidemic starts because the specific germs have become more virulent or disease-producing; some individuals die because their microbes are highly virulent, while others are spared because theirs are less so; the disease spreads locally or widely according to the powers of the germs; stops when they begin to lose their potency; and reappears again sooner or later when a new increase in virulence is attained. The germ theory, therefore, explains epidemics entirely in terms of fluctuations in microbic virulence.

More than forty years of bacteriological research have since demonstrated that the experiments upon which this theory is based were not well-controlled and that their application is subject to considerable limitation. Furthermore, statisticians and clinicians are pointing out the close association of prevalence

of infection with season, diet, and other environmental conditions. The resisting mechanisms of the animal host, hereditary or acquired, racial or individual, also are now recognized as playing a part. Apparently, therefore, some element of truth still remains in the pre-bacteriological theories of "epidemic constitution."

Instead of reviewing in detail these recent tests and observations, I should like to speak of our own work in experimental epidemiology, so-called because its purpose is to study the mode of spread of epidemic diseases, and because its method is truly experimental.[1]

The history of experimental epidemiology is brief. In 1918 Topley induced epidemics of mouse typhoid experimentally in his laboratory in London, and studied the conditions under which these outbreaks occurred.[2] At about the same time, Flexner, assisted by Amoss, began similar studies at the Rockefeller Institute in New York. Since then Topley has continued to work actively in England, and we in this city. Three years ago Neufeld, Director of the Robert Koch Laboratory in Berlin, and his associates, began experimental epidemiological investigations,[3] and at present, in America, there are five, and perhaps other laboratories, in which these same problems are being considered.

To study epidemics experimentally, it is necessary to choose some native animal microbic disease resembling a human infection. Then at least three procedures are indicated: 1) studying the disease as it occurs spontaneously in nature; 2) inducing its various endemic and epidemic phases experimentally in the laboratory, and 3) determining and measuring the factors which cause the disease to vary in amount and severity.

We have been concerned with five native animal infections; three in mice, one in rabbits, and one in chickens. Two are intestinal and three respiratory in origin; mouse typhoid, caused by a paratyphoid organism; mouse typhoid, caused by a food poisoning, enteritidis-like bacillus; mouse pneumonia, due to a

[1] These studies are published in the *Journal of Experimental Medicine.*

[2] Professor Topley's reports may be found in the *Journal of Hygiene.*

[3] The work from Professor Neufeld's laboratory has been published in the *Zeitschrift für Hygiene.*

capsulated organism of the Friedländer group; rabbit colds and pneumonia, caused by the plague-like pasteurella organism; and fowl colds and pneumonia, known as roup and fowl cholera, due also to a plague-like bacillus of the pasteurella group. Each has been studied as it occurs spontaneously; each has been induced experimentally in the laboratory and there analyzed under carefully controlled conditions.

The technique for observing the *spontaneous* disease in an animal community consists in familiarizing ourselves over long periods of time with the amount and type of clinical infection, and the number of specific deaths and nature of the lesions, and relating this information to the prevalence of the specific bacteria in the population. The technique used in the analysis of the *experimental* epidemics is a very special one which has two important requirements; namely, maintaining all conditions as near as possible to those occurring spontaneously in nature, and second, removing all disturbing and unknown variables.

The results of our observations on the spontaneous diseases enabled us to plan the laboratory epidemics more successfully. They gave us information concerning the various types of clinical infection and the relative amount of each, of seasonal fluctuations in type and severity of disease, and knowledge of the amount and distribution of the specific bacteria available to the population.

The most significant results, however, were obtained from studies of the experimental laboratory epidemics. Here, as elsewhere, we found the amount and severity of infection in a community to depend upon three factors: the disease-producing power or virulence of the microbe, the numbers of microbes available, and the resisting powers of the population concerned. Our ultimate task therefore lay in the measurement of these factors during various epidemic and endemic phases of each disease.

Before discussing the results of these measurements, one further word concerning technique is necessary.

Virulence, dosage, and host susceptibility are measured by administering specific organisms to animals and noting their reactions and duration of life. Formerly, in such tests, no control measures were employed. For example, culture A from a

human being was administered intraperitoneally to one mouse, and culture B in similar quantity to another. If the first mouse was found to live longer than the second, culture A was considered to be less virulent. At the present time, however, we know that microbes given to a foreign host behave in a manner quite different from when administered to their native host; that given by an abnormal portal of entry, their effect is in no way comparable to that when administered by the normal route of infection; that differences in individual susceptibilities of animals make it obligatory to use sufficiently large numbers for each test; and finally that differences in actual numbers of organisms administered exert markedly different effects. Therefore, titrations of virulence, of dosage effect, and host susceptibility differences, to be of any epidemiological significance, that is, to throw light on the natural mode of spread of disease, must be made *with organisms administered in type pure culture, in known numbers, to their natural host by way of the normal port of entry!*

We have titrated the virulence of organisms concerned with four of these native animal infections, the paratyphoid and enteritidis mouse typhoid, mouse Friedländer pneumonia, and rabbit colds and pneumonia. The cultures have been obtained from various animal populations in which the specific diseases were spreading spontaneously, or as a result of experimental procedures. We have compared the virulence of cultures taken from pre-epidemic periods, epidemic periods, and post- and inter-epidemic times. Organisms recovered from animals which have died acutely during severe outbreaks have been compared with others taken from surviving healthy carriers. The effect of animal passage on virulence has also been tested.

Throughout, our results have been consistent in that we have found no differences in the pathogenicity of type pure cultures recovered from pre-epidemic, epidemic, post- or inter-epidemic phases of these infections. Animal passage, likewise, had no changing effect on the disease-producing powers of the microbes. The bacteriophage phenomenon, present in the mouse enteritidis infection, and "bacterial variation" phenomena which occurred in all but the mouse paratyphoid disease, were found to play no part in determining the amount and severity of these outbreaks.

Hence we concluded that in the diseases studied, the microbic virulence factor is relatively constant.

Analysis of the dosage factor revealed that, in general, an increase in numbers of bacteria given to groups of animals is followed by an increase in morbidity and mortality. Furthermore, we found that by choosing proper doses of mouse typhoid or mouse Friedländer organisms and administering them to groups of mice, there resulted amounts and rates of mortality which corresponded to those occurring among our special populations during spontaneous epidemics of these diseases. Apparently, therefore, epidemics were caused merely by bringing animals in contact with the requisite amount of the specific organisms.

This hypothesis was tested further among our special populations of animals, in which spontaneous epidemics were occurring, by determining whether each outbreak was preceded by a demonstrable increase in numbers of specific bacteria available. Thus, by counting the typhoid bacteria present in the sawdust bedding, and the numbers of nasal carriers of the Friedländer organisms, we found that there was a very great rise in the amount of bacteria available to the herd before each outbreak. Wave-like fluctuations in dosage preceded similar mortality waves by an interval of time corresponding to the incubation period of the disease. We concluded, therefore, that the presence of a proper dosage of microbes is the essential cause of epidemics of these four native animal diseases.

In titrating the third factor concerned in the spread of epidemic diseases, host resistance, we were able to demonstrate consistent and significant differences in racial susceptibility to infection. Furthermore, individuals were found to differ in their ability to resist disease. For example, if a number of rabbits was given intranasal instillations of the pasteurella organism, some developed pneumonia and septicemia and died, others showed merely local rhinitis, sinusitis, or otitis media, while still others proved to be carriers, or entirely refractory. Differences in the resisting powers of individual animals were further demonstrated by selective breeding experiments, whereby relatively resistant or susceptible strains were developed.

The amount of racial and individual resistance of animals

was found to be markedly affected by dietary and atmospheric conditions. Thus, mice fed on the so-called McCollum standard diet, or on a ration containing cod liver oil, proved far more resistant to the paratyphoid and Friedländer infections than other groups fed on the usual bread and milk formula. Hence we sought to determine whether in the special populations of animals under observation there were fluctuations in resistance to the specific infections, which might account for the increased dosage and epidemic outbreaks observed.

Unfortunately, we have not been able to devise a technique suitable for the direct measurement of population resistance, but we have succeeded in altering this factor experimentally and observing the effect of such a procedure on the course of disease. By subjecting a community of rabbits to daily fluctuations in temperature of about 50° F., we apparently brought about a marked increase in the number of carriers of the pasteurella organisms and subsequently in the amount and severity of snuffles and pneumonia. And by keeping a part of this population on a partially restricted diet, we noted at all times a carrier rate greater than that of the remainder of the community not so treated. The carrier rate and amount of Friedländer and enteritidis infection in the special populations of mice were strikingly influenced by substituting the beneficial McCollum diet for the usual ration. And when the daily increments to these populations were made up of susceptible races of mice, rather than the usual relatively resistant strain, the amount of disease increased immediately. Apparently, therefore, a lowering of population resistance is followed by an increase in the number of virulent organisms and the amount of disease present in the community, while an enhancement in the communal powers of defense leads to a corresponding decrease in dosage and mortality.

We conclude that in the native animal diseases studied, microbic virulence does not fluctuate and that epidemics are incited directly by an increase in the numbers of specific bacteria available to the population. We believe this increase in dosage is the result of changes in host resistance and that these changes may be brought about in two ways, according to whether the specific organisms are already present in the community, or

gain entrance to it from without. If the bacteria are exogenous, they ordinarily meet with a population of little or no resistance, multiply, and disseminate rapidly, and thus cause a severe epidemic. If, on the other hand, the pathogenic microbes are already present in a given community, an increase in dosage takes place when population resistance is lowered, through births, migration and fluctuations in seasonal, dietary, and other environmental influences.

At present we do not wish to generalize too far, nor to extend our conclusions to human disease, but we do wish to stimulate further thought on these questions. Is there any proof that human pathogens change in virulence? May not typhoid and dysentery outbreaks from food or water contamination, pandemic influenza, plague and cholera of the middle ages, tuberculosis and exanthemata of isolated communities have been due to foreign organisms coming in contact with a highly susceptible population, thus leading to tremendous increase in available dosage? And may not endemic pnuemonias, exanthemata, common colds, Oriental plague, cholera, and malaria be caused by lowering of population resistance to organisms already present in the community, leading thereby to an enhancement of dosage?

Careful experiments, well controlled, are needed before we can venture an answer to these questions. But if it prove that the amount of population resistance does determine the amount or dosage of virulent bacteria present in a community, and thus controls the prevalence of infectious disease, then for the first time we are shifting the responsibility for epidemics from the field of the mysterious to that of an understandable, concrete series of events; we are approaching the time when we may hope for control over pandemic outbreaks, and are justifying experimentally any and all attempts toward personal and social hygiene. From the clinician and health official we shall need aid in the further pursuit of this problem. I speak tonight for this and for your renewed interest in epidemiology.